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PROGNOSIS OF INTRATHORACIC SARCOIDOSIS IN ENGLAND

A REVIEW OF 136 CASES AFTER FIVE YEARS' OBSERVATION

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Early in 1960 I surveyed the records of 230 patients with sarcoidosis whom I had first seen up to the end of the previous year, with special reference to the role of *Mycobacterium tuberculosis* in aetiology, and in discussing them described the diagnostic criteria adopted (Scadding, 1960). A total of 136 first came under my observation before the end of June, 1955, and in the autumn of 1960 I endeavoured to complete the review of this group, first seen five years or more previously, by obtaining information about the current state of those among them who had passed out of my supervision. This paper describes the result of this review, with special reference to prognosis in relation to the intrathoracic changes.

The patients were first seen with various types of intrathoracic change, and at widely differing intervals after the probable time of onset of sarcoidosis. An earlier review of them (Scadding, 1956) had suggested that prognosis might be related to the type of intrathoracic change then found, even among those who showed no evidence of fibrosis at that time. For these reasons I have divided the patients into four groups according to the type of change in the chest radiograph when I first saw them:

Group 1: 32 patients; enlarged hilar lymph-nodes only.

Group 2: 40 patients; mottled shadowing in the lungs with enlarged hilar lymph-nodes, either present or known to have been present in the past.

Group 3: 37 patients; mottled shadowing in the lungs, without present or available past evidence of enlargement of hilar lymph-nodes.

Group 4: 27 patients; radiographic and clinical features suggesting fibrosis, usually in addition to mottled shadowing.

Groups 2 and 3 and groups 3 and 4 are not, of course, sharply demarcated from each other. It is not possible to be certain that none of the patients in group 3 had ever had enlarged hilar lymph-nodes, since such certainty would be possible only if a normal chest radiograph were available shortly before the first abnormal one; this group is therefore likely to contain, in addition to patients in whom there was in fact no stage of enlargement of hilar nodes, some in whom this stage passed without symptoms and had subsided by the time the disease was first detected. In three of them there was a record of a normal chest radiograph within three months, one year, and one year of the first abnormal one, and in 10 others there were and had been no symptoms at the time of the abnormal radiograph which was the first evidence of the disease, making it highly probable that there was in fact no stage of hilar node enlargement. The distinction between groups 3 and 4, consisting in the judgment on clinical and radiological grounds that in group 4 irreversible changes were present at the beginning of observation, cannot be regarded as precise, but in most cases decision was not difficult.

The sex distribution within these four groups is shown in Table I, together with the ages, expressed as means and ranges, when the patients first came under my observation; the estimated duration of the disease at the beginning of the observation period; and the estimated age at the time of onset of sarcoidosis, deduced from this estimated duration. In some cases the onset was marked by a definite symptom—for example, erythema nodosum or acute iridocyclitis; in others a less definite symptom was taken to indicate the onset; and in others, without symptoms, the date of the first abnormal radiograph was taken as the time of onset. As would be expected, the duration of the disease at first observation was least in group 1 (mean 6 months) and greatest in group 4 (5½ years). In groups 2 and 3 it was very similar (1½ and 1¾ years respectively); this shows that the failure to find evidence of enlargement of hilar nodes in group 3 was not due to the patients having come under observation later in the course of the disease than those in group 2.

TABLE I.—*Age-and-sex Distribution of* 136 *Patients with Sarcoidosis. Age at Time of Onset is Estimated from the Age When First Seen and the Estimated Duration of the Disease at that Time*

Group	No. of Patients			Age in Years when First Seen		Estimated Duration of Disease when First Seen (Years)		Age in Years at Estimated Time of Onset	
	Total	M.	F.	Mean	Range	Mean	Range	Mean	Range
1	32	15	17	28	16–47	6 12	0–2	28	16–47
2	40	11	29	30	19–51	1 6/12	6/12–11	28	18–50
3	37	17	20	34	18–54	1 9 12	1 12–5	32	18–52
4	27	13	14	41	25–55	5 6 12	6 12–20	36	22–52
Total	136	56	80	33	16–55	2 4/12	0–20	31	16–52

The condition of the patients in these four groups five years after they first came under my observation is summarized in Table II.

TABLE II.—*Condition of 136 Patients with Sarcoidosis at End of Five Years' Observation, Grouped by Condition at Beginning of Observation*

Group	Total No.	Condition after Five Years' Observation					
		Normal X-ray	Abnormal X-ray			Dead	
		No Symptoms	No Symptoms	Mild Symptoms	Severe Symptoms	Sarcoidosis	Other Cause
1	32	27	4	1	0	0	0
2	40	23	2	11	3	0	1
3	37	16	6	8	6	0	1
4	27	0	0	9	11	6	1

Group 1: Enlarged Hilar Nodes Only

The 32 patients in this group came under my observation at intervals varying from three weeks to two years after the first evidence of the disease. Twenty-three were followed for the full five years. Four were last seen after three years', one after two years', and four after one year's observation; all these were then free from all symptoms and signs of disease and with normal chest radiographs. Since no patient who attained a normal radiograph has later shown evidence of recurrent disease under further observation, the presumption that these nine patients remained well is high, and in Table II they are classed as well, with normal radiographs at five years. Including these, 27 (82%) of the 32 patients were left with no evidence of disease at five years. Two had some abnormal shadowing in the lungs, without symptoms, and three still had enlargement of hilar nodes, two without symptoms and one with slight dyspnoea on exertion and undue tiredness. During the five years' observation a total of 10 of the 32 patients developed mottling in the lung fields, at intervals varying from 1 to 10 months from the detection of the enlarged hilar nodes. Of these, eight showed complete resolution and are included among 27 without evidence of disease at five years; in the two who showed residual shadowing at five years it was interpreted at the end of this time as diminishing sarcoid infiltration in one, and as insignificant residual fibrosis in the other.

Twelve of the patients were followed longer than five years, for periods up to 10 years. Ten of these had been free from residual abnormality at five years, and two had had persistent enlargement of hilar nodes; all remained unchanged under further observation, the two with persistently enlarged hilar nodes having been last seen 6 and 10 years from the apparent time of onset.

Of 10 patients whose illness started acutely with erythema nodosum (7) or acute polyarthritis (1) or both these manifestations (2), none had residual changes, as compared with the 22 with other modes of onset, who included all five of those with residual abnormalities at five years. Two patients developed painless subcutaneous nodules near the ulnar borders of the forearms within a few weeks of erythema nodosum. These were moderately firm and elastic, about 1 cm. in diameter: one was found in one patient and several on both arms in the other. Histologically they showed the typical sarcoid structure; in both cases they subsided spontaneously within three months, and both patients were well, with normal radiographs, at five years.

Iridocyclitis was observed in 6 of the 32 patients. In five of these it was the sole extrathoracic manifestation of sarcoidosis, and in the sixth it was accompanied by transient sarcoid infiltrations of the skin over the shins. Four of the six, including the patient with skin lesions, showed complete resolution of all sarcoid lesions; the other two had radiographic abnormalities without symptoms at five years, consisting in persistent mottling in one and persistent hilar node enlargement in the other.

Group 2: Lung Shadows with Enlarged Hilar Nodes

The 40 patients in this group first came under my observation at a mean interval of one and a half years after the apparent onset of the disease. Thirty-four were followed for the full five years. Of the remaining six, one was followed for four years, four for three years, and one for two years. At this time they were all well, with normal chest radiographs, and, for the reasons given above, I have assumed, in compiling the data on which Table II is based, that they remained so throughout the rest of the five-year period. By the end of five years' observation 16 others had attained a normal chest radiograph, making 23 in all (58%) with complete radiographic resolution and freedom from other signs of sarcoidosis. Of the remaining 17, two were symptom-free but still had some faint mottling in the lungs, the hilar nodes having subsided; 11 had mild symptoms, and three had moderate to severe symptoms with radiographic abnormalities in the lungs; and one had died of an unrelated disease. In the 11 with mild symptoms the abnormality consisted in persistence of enlargement of hilar nodes only in one, and of both enlarged hilar nodes and mottled shadowing in the lungs in two, and in evidence of limited inactive residual fibrosis in eight. In the three with more severe symptoms, of which the chief was dyspnoea on exertion, there was clear evidence of fibrosis, with continued activity of sarcoidosis in two. The cause of death in the patient who died was carcinoma of the liver; at the time of death, 11 years from the onset of sarcoidosis, there was some residual shadowing in the chest radiograph, probably fibrotic, but there were no serious symptoms attributable to sarcoidosis.

Twenty patients have been followed for longer periods, up to 10 years. Of these, 16 have remained unchanged since the end of the five-year period; two have improved—one who had persistent lung mottling at five years having shown resolution by the eighth year, and one with radiographic evidence of insignificant fibrosis and mild symptoms at five years having lost her symptoms by the end of 10 years; and two have died of sarcoidosis. Of the latter two, one died of respiratory insufficiency from progressive fibrosis of the lungs 11 years after the estimated time of onset of the lung changes and 21 years after the iritis which was probably the initial symptom of sarcoidosis; and one died, 12 years after the iritis which was the first evidence of sarcoidosis, from uraemia due to hypercalcaemic nephropathy, with moderate but non-progressive fibrosis in the lungs.

Among the 23 patients whose lungs were radiographically clear after five years' observation, 18 had shown no evident extrathoracic manifestation of sarcoidosis, four had iridocyclitis, and one developed transient papular skin sarcoids on the legs after the intrathoracic manifestations had subsided. Among the 17 with persistent radiographic abnormalities, only five had no evident extrathoracic lesion, five had iridocyclitis, and no fewer than seven had sarcoidosis of the skin, of whom one had also gross hepatosplenomegaly. In group 2, as in group 1, an onset with erythema nodosum

seemed to be of good prognostic import. The illness started with erythema nodosum in seven patients, of whom six attained radiographically clear lungs.

Group 3: Lung Shadows Without Definite Evidence of Enlarged Hilar Nodes

The 37 patients in this group were first seen at a mean interval of one and three-quarter years from the apparent onset of the disease. Thirty-two were followed for the full five years. Of the remaining five, four were well, with a normal chest radiograph, when they were last seen, three after three years and one after two years, and one had limited fibrosis with no disability at three years. In Table II these five patients have been assumed to have remained unchanged for the rest of the five-year period. With these assumptions, 16 patients (43%) had attained a normal chest radiograph within five years. Six others had no symptoms, but some persistent radiographic abnormality, consisting of persistent mottling in one and slight residual inactive fibrosis in five. Fourteen had radiographic changes suggesting fibrosis, symptoms being mild in eight and severe in six. One died of mediastinal lymphosarcoma towards the end of five years' observation, nine years from the first symptoms of sarcoidosis; at the time of death there was moderate fibrosis in the lungs.

Twenty patients have been followed for longer periods, up to 13 years. Of these, 19 have remained unchanged—nine with clear radiographs, three with slight fibrosis and no symptoms, and seven with fibrosis and symptoms, mild in one and severe in six—and one has persistent mottling without symptoms or obvious fibrosis. The patient with persistent mottling has been under observation for 10 years from its first discovery. One patient with fibrosis deteriorated under further observation, and when last heard of after 13 years' observation was seriously ill with congestive heart failure.

Extrathoracic sarcoid changes were found less often in group 3 than in group 2. Of 16 patients with radiographically normal lungs at five years, two had had eye and one skin involvement; one developed heart-block, presumably from a sarcoid granuloma interrupting the bundle of His. Of the other 21, one had eye and three skin involvement, and one had gross hepatosplenomegaly. Erythema nodosum occurred in only one patient, whose lung changes resolved completely.

Group 4: Fibrosis Thought to be Present at Beginning of Observation

The 27 patients in this group first came under my observation at a mean interval of five and a half years from the probable time of onset of the disease. They are, of course, a selected group, many of whom were referred to me after prolonged periods of observation by other physicians because of an unfavourable course. It was possible to obtain evidence of an initial stage of enlargement of hilar lymph-nodes, accompanying or preceding the shadowing in the lungs, in only seven of them. In eight there was an available radiograph very early in the clinical course showing lung shadowing only, making it probable that there had been no stage of enlarged hilar nodes; and in the remaining 12 there was insufficient evidence on which to base an opinion whether there had been such a stage.

Of the 27 patients, 25 were followed for the full five years or to the time of death. The remaining two were followed for three years; at the beginning of the observation period they had had non-progressive fibrosis without evidence of activity of the sarcoidosis and with only slight disability, and their condition remained unchanged during the three years' observation. Accordingly in compiling the data on which Table II is based I have assumed that they remained unchanged for the rest of the five years. At the end of this time nine patients had mild symptoms, not preventing them from leading a normal life, 11 had more severe symptoms, though all but three were able to continue in employment or housework, and six had died of sarcoidosis and one of a cerebral haemorrhage. Of the 20 patients who survived, 10 appeared to have remained unchanged, three to have deteriorated, and seven to have shown some improvement during the five years' observation. In those who showed improvement, this could be attributed to resolution of reversible elements which had been present in the lung changes at the beginning of this period. Five of the patients who died of sarcoidosis did so in the 6th, 9th, 10th, 18th, and 25th year of the disease; in the sixth it was not possible to date the onset, since when she first consulted a physician, four years before death, established fibrosis of indeterminate duration was already present (Clinico-Pathological Conference, 1950).

Ten patients have been followed for longer periods, up to 12 years. In nine, there was no important change during this further observation, and one died from sarcoidosis in the seventh year of my observation and the fourteenth of the disease.

Extrathoracic sarcoidosis, especially of the skin, was frequent in group 4. Eight patients showed skin sarcoidosis, including three with lupus pernio and two with infiltrated scars. One other patient had multiple subcutaneous sarcoid nodules in the fingers. One had a sarcoid nodule in the breast. Two developed evidence of cardiomyopathy; since both are still alive, it has not been possible to determine with certainty whether this is due to sarcoid infiltration of the myocardium. Four have multiple bronchostenoses of the type described by Citron and Scadding (1957). No patient in group 4 had erythema nodosum at the onset of the disease or subsequently.

Corticosteroid Treatment

Observation both of the present series and of subsequent cases of sarcoidosis has led me to the firm opinion that corticosteroids have no effect upon the principal criterion of prognosis adopted in this analysis—namely, the attainment and maintenance under prolonged observation of a normal chest radiograph with freedom from symptoms. Certainly, manifestations of the disease can be suppressed while they are in a reversible stage, presumably represented pathologically by epithelioid cell granulomata without fibrosis. When in such a case the corticosteroid treatment is withdrawn, the disease may either return to its former state, seem to have been "cured" in that it does not reappear, or recrudesce to a worse state than formerly. The most reasonable interpretation of these facts seems to be that the effect of corticosteroid treatment on the disease process is purely suppressive, and that in those cases in which the disease appears to have been "cured" it would have regressed gradually even if untreated; in those in which it reappears in its former state it would have remained unchanged; while in those in which a

" rebound " to a worse state occurs after withdrawal it would have deteriorated.

When irreversible fibrotic changes in the lungs, or a very dense infiltration with sarcoid tubercles, have caused dyspnoea, unproductive cough, and other symptoms, these may be relieved to a variable degree by corticosteroid treatment. In some cases this relief constitutes a sound indication for such treatment, which may need to be continued indefinitely. There are probably two elements in the causation of such relief: the suppression of the specific cellular reaction in still active sarcoid infiltration, and favourable effects on secondary phenomena such as airway obstruction from mucosal swelling and bronchospasm. Extrapulmonary indications for corticosteroid treatment include hypercalcaemia, certainly when it produces symptoms and probably if the serum calcium remains above 12 mg. per 100 ml., and eye changes which cannot be controlled by local treatment.

This statement of my present views is necessary for two reasons as a preamble to the following description of the observed effects of corticosteroids in those patients in the present series who received such treatment. First, it explains why in the discussion of prognosis I have not thought it necessary to mention separately the minority of treated patients. And second, it provides an occasion to emphasize that the period covered by the present survey includes the time when corticosteroids were first available clinically, and that, since the experience recounted is the earlier part of that upon which the views stated above are based, many of the patients who received corticosteroids would be treated differently or not at all if they came under observation to-day.

In group 1, only three patients received cortisone for periods of three to eight weeks, soon after this hormone came into general use and before the generally favourable prognosis of patients with bilateral hilar lymph-node enlargement was fully realized. In two there was a slight reduction in size of the enlarged hilar nodes during the administration of cortisone, followed by return to the previous size on withdrawal, and spontaneous resolution within the next two years. In the third the cortisone had no effect on the enlarged nodes, which still remained enlarged, though somewhat diminished in size, after eight years' observation. It is clear, therefore, that corticosteroid treatment did not influence the outcome, and that there is no indication for such treatment in this group.

Short-term Treatment of Patients with Generalized Lung Changes

Twenty-eight patients in groups 2, 3, and 4 received cortisone for periods of three to eight weeks at the time when its effects were being explored. In three patients with established fibrosis no effect, even on the symptoms, was observed. In 25 there was partial or complete suppression of manifestations of the disease during treatment, followed by their return on its withdrawal; in 12 of these there was subsequent spontaneous resolution, and in the remaining 13 the lung changes proved persistent. Six of these 13 later had prolonged treatment with corticosteroids, and are included in the group discussed below.

Prolonged Treatment

Twenty-nine patients received prolonged treatment—20 in groups 2 and 3, and 9 in group 4. Groups 2 and 3 are considered together, since in them there was thought to be some possibility of resolution. Group 4, in which resolution was not to be expected, is considered together, since in them there was thought to be some possibility of resolution. Group 4, in which resolution was not to be expected, is considered separately.

Among the 20 patients in Groups 2 and 3, in only seven was treatment discontinued electively after substantial resolution and without subsequent recrudescence. The mean period of treatment of these seven patients was two years, with a range of nine months to four years. Two of them were left with clear lungs, and two with slight residual fibrosis but no disability; in two there was some resolution at the end of 20 months' and 32 months' treatment, and this resolution continued after the cessation of treatment, the final result being slight fibrosis with mild dyspnoea. In the seventh patient there was little change in the lungs, which showed fibrosis confined to the middle zones with little disability; prednisolone was given for the relief of pain and swelling due to involvement of the phalanges, the improvement produced being maintained when treatment was withdrawn after four years. In three patients the lung changes have progressed to irreversible fibrosis in spite of prolonged corticosteroid administration, but treatment with small doses is being continued after five, five, and six years because withdrawal gives rise to increase in dyspnoea, cough, and lassitude.

In two patients several periods of treatment during the course of two and three years respectively caused temporary suppression of radiographic shadows and relief of symptoms followed by recrudescence; after cessation of treatment, fibrosis of limited extent, apparently inactive and stable, was left, with little disability. In one no change in radiographic appearances resulted from periods of four months' and 10 months' treatment, but one year after the end of the second period of treatment partial spontaneous clearing of the shadowing was observed. In two patients there was no effect from treatment for three months in one and two periods of four months in the other; the latter developed a large gastric ulcer during the second period of treatment. In one patient skin lesions scattered over the trunk, forehead, and scalp were suppressed during three periods of treatment for seven weeks, two years, and 14 months, but recrudesced within a month or two of cessation of treatment; this patient eventually died of a mediastinal lymphosarcoma.

In the remaining four patients corticosteroid treatment was used for the control of hypercalcaemia. In one it proved possible to withdraw the hormone after 18 months, without return of the hypercalcaemia; two are continuing with small dosage of prednisolone, which remains necessary to control hypercalcaemia after more than seven years; and one, who had commencing renal insufficiency when treatment was started, required for the control of hypercalcaemia corticosteroid dosage causing important side-effects, and died in uraemia after three years' treatment. In all four patients treated for hypercalcaemia there was no more than a slight suppressive effect on the lung changes.

In summary, among these 20 patients there were only two who, after elective cessation of prolonged administration of a corticosteroid which had caused suppression of the radiographic shadows in the lungs, were left with clear lungs. It is difficult to claim that this is a better end-result than might have followed an entirely expec-

tant policy; although there can be no doubt of the partial or complete relief of symptoms, when present, and the suppression of radiographic shadowing in most cases during corticosteroid administration.

Among the nine patients with established fibrosis in group 4 who were treated, four experienced sufficient symptomatic relief to justify continued administration of small doses. One of these has been treated continuously for five and a half years; one was treated for nearly three years, deteriorated four years later, and has now been treated again for over one year with worthwhile symptomatic relief; and two—Cases 1 and 2 of Citron and Scadding (1957)—have multiple bronchostenoses and still require small doses of prednisolone to maintain symptomatic improvement after seven and six years. One other patient with multiple bronchostenoses —Case 3 of Citron and Scadding (1957)—experienced some symptomatic relief during two and a half years' treatment, relapsed to her former state when it was withdrawn, but did not wish for further treatment and remained unchanged two years later. Two patients experienced no symptomatic relief after treatment for 18 and 12 months, and the corticosteroid was withdrawn without incident. In the remaining two patients treatment was given mainly for the control of extensive skin lesions. Both of them were middle-aged women, with severe fibrosis in the lungs, and both developed hypertension with corticosteroid treatment. This gave rise to a difficult situation, since the skin lesions responded only to doses of corticosteroids which caused hypertension. One died of respiratory insufficiency after three and a half years, and the other was very severely disabled at the end of five years' observation with uncontrolled and extensive skin lesions, which on several occasions spread obviously after withdrawal of corticosteroid treatment which was given repeatedly in various forms and dosages in attempts to control them. In neither of these patients was dyspnoea from the lung fibrosis relieved in any way.

In summary, four out of nine patients with established fibrosis in the lungs experienced enough symptomatic relief to justify the continuance of long-term administration of a corticosteroid in small dosage (usually 10 to 15 mg. of prednisolone daily). Treatment of a small number of cases with skin changes indicated clearly the purely suppressive nature of the effects of corticosteroids in sarcoidosis.

These general views on the effect of corticosteroids on the evolution of sarcoidosis are in agreement with those of Sones and Israel (1960), who, in describing the course of 211 patients did not think it necessary to discuss separately the 93 among them who received corticosteroid treatment. They state that in their opinion, "although corticosteroids definitely modify the clinical symptoms and pathologic changes, the ultimate outcome of the disease is not as a rule significantly altered by the use of these agents."

Prognosis of Lung Changes in Relation to Extrathoracic Changes

Table III shows the numbers of patients in the various groups whose illness started acutely with erythema nodosum or acute arthralgia, subdivided into those who did and did not attain radiographic clearing. As in previously reported series, erythema nodosum occurred more often in women than in men, 13 women and 5 men being affected. Moreover, in three of the five men the acute illness at the beginning was characterized predominantly by a febrile arthralgia, with atypical erythema nodosum. It is clear that erythema nodosum is significantly associated with enlargement of hilar lymph-nodes, having occurred in 17 out of 72 patients in whom the hilar nodes were known to have been enlarged, and in only 1 out of 64 in whom there was no evidence of such enlargement. It is also highly significantly related to the ultimate attainment of a clear chest radiograph.

TABLE III.—*Incidence of Acute Onset With Erythema Nodosum or Rheumatism in Patients Whose Intrathoracic Sarcoidosis Did and Did Not Attain Radiographic Clearing, Showing the Favourable Prognostic Significance of this Type of Onset. (For All Groups Combined, $\chi^2=15.2$; $P<0.001$)*

Group	Well with Normal X-ray at 5 Years		All Others	
	Total No.	Erythema Nodosum at Onset	Total No.	Erythema Nodosum at Onset
1	27	10	5	0
2	23	6	17	1
3	16	1	21	0
4			27	0
Total	66	17	70	1

On the other hand, sarcoid lesions of the skin appear to constitute an unfavourable prognostic sign (Table IV). Skin sarcoidosis was observed in 21 patients. Two of these had, in addition to sarcoid lesions of previously normal skin, infiltration of old scars, and two showed infiltration of scars only. Of the 70 who still had radiographic changes at five years or died, 18 had skin lesions, as compared with only 3 out of the 66 who attained radiographic resolution. This difference is significant at the 1% level.

TABLE IV.—*Incidence of Sarcoidosis of the Skin in Patients Whose Intrathoracic Sarcoidosis Did and Did Not Resolve Within Five Years of Observation, Showing that in the Presence of Skin Lesions the Chance of Radiographic Clearing is Less. (For All Groups Combined, $\chi^2=9.9$; $P<0.01$)*

Group	Well with Normal Radiograph at 5 Years		All Others	
	Total No.	Skin Sarcoidosis	Total No.	Skin Sarcoidosis
1	27	1	5	0
2	23	1	17	7
3	16	1	21	3
4			27	8
Total	66	3	70	18

Table V shows the incidence of eye lesions producing clinically evident symptoms. It is clear that these are randomly scattered through all groups and between those who did and did not attain radiographic resolution, and thus have no prognostic significance in relation to lung changes. The mean incidence of 15% is much less than that reported, also from London, by Smellie

TABLE V.—*Incidence of Clinically Evident Eye Lesions in Patients Whose Intrathoracic Sarcoidosis Did and Did Not Resolve Within Five Years of Observation*

Group	Well with Normal X-ray at 5 Years		All Others	
	Total No.	Eye Lesions	Total No.	Eye Lesions
1	27	4	5	2
2	23	4	17	5
3	16	2	21	1
4			27	3
Total	66	10	70	11

and Hoyle (1960). The difference is almost certainly to be explained by the inclusion in my series of only those cases in which the ocular changes produced symptoms and by the fact that at the time when I first saw these patients I had no special link with a department of ophthalmology.

Table VI shows the incidence of other extrapulmonary changes in the various groups. Of these, only generalized enlargement of superficial lymph-nodes (10 cases) and slight to moderate enlargement of the spleen (23 cases) were observed with sufficient frequency to

TABLE VI.—*Extrapulmonary Lesions, Other than Sarcoidosis of Skin and Eyes, Observed in* 136 *Patients with Intrathoracic Sarcoidosis*

	Group				Total	Chest Radiograph after 5 Years	
	1	2	3	4		Clear	Not Clear
Generalized superficial lymphadenopathy		5	2	3	10	4	6
Gross hepatosplenomegaly		1	1		2		2
Spleen palpable	4	7	8	4	23	11	12
Subcutaneous nodules	2			1	3	2	1
Infiltration of vestibule of nose			1		1	1	
Osteitis of bones of hands		1	1		2	1	1
Nodule in breast				1	1		1
Heart-block			1		1	1	
Cardiomyopathy—? sarcoid				2	2		2
Parotid swelling	1	1			2	2	
Swelling of lacrimal gland		1			1	1	
Facial palsy	1	1			2	1	1
Hypercalcaemia (causing symptoms)		2	2		4		4

justify an attempt to assess their prognostic significance. Since they occurred with about equal frequency in the 66 patients who did and the 70 who did not attain radiographic resolution, it is clear that in this series their presence did not affect the outlook in relation to the intrathoracic changes. The only other point possibly worth noting is that three serious manifestations—gross hepatosplenomegaly (2 cases), cardiomyopathy (2 cases), and hypercalcaemia causing symptoms (4 cases)—were in all instances associated with non-resolution of lung changes.

Calcification was observed to develop in lung or hilar nodes in seven certainly, and in another 11 probably, of the 136 cases (Scadding, 1961). This event tended to occur in patients with extensive intrathoracic changes, not undergoing complete resolution (even apart from the calcification). None of the seven with undoubted new development of calcification, and only two of those in whom it was probable, attained complete radiographic resolution of lung changes.

Histological evidence of involvement of the main bronchi was obtained in eight cases. In two patients in group 2 biopsy of the normal-looking mucosa in a main bronchus distorted by bronchopulmonary and hilar-node enlargement showed subepithelial infiltration with epithelioid-cell tubercles; both of these eventually were left with non-disabling residual fibrosis in the lungs and no bronchial stenosis. Six patients were first seen with bronchostenoses, four with the multiple type described by Citron and Scadding (1957) and two with narrowing of a single bronchus. All these showed atypical epithelioid-cell tubercles and fibrosis in biopsies from the narrowed bronchi. As would be expected, they were all left with permanent radiographic abnormalities and some disability.

Three patients had had frankly tuberculous manifestations—apical pulmonary tuberculosis, cervical adenitis, and pleural effusion containing tubercle bacilli—18 months to 4 years before sarcoidosis became evident. In 10 others tubercle bacilli were found during the course of sarcoidosis, on a single occasion in eight and twice in the other two, without any change in the clinical or radiological picture. The prognosis in these cases proved to be similar to that of the whole series; I have discussed this point elsewhere in relation to the larger series of 230 cases mentioned above (Scadding, 1960). Late in the course of the disease four patients underwent a change in clinical picture to that of caseating tuberculosis, with increase in tuberculin sensitivity and the appearance of tubercle bacilli in the sputum.

Ten women—three in group 1, four in group 2, and three in group 3—became pregnant during the five years' observation, two of them twice, making 12 pregnancies in all. Three of these pregnancies occurred after complete radiological resolution of the lung changes, and the lungs remained clear. Three occurred at a time when lung changes appeared to be resolving; the lungs became completely clear during the pregnancies and remained so afterwards. In two women faint abnormal mottling in the chest radiograph remained unchanged during and after pregnancy. Three women became pregnant, one of them on two occasions, when they showed widespread mottling in the chest radiograph; during these four pregnancies the shadows resolved partially or completely, only to reappear three to six months afterwards. All except one of the pregnancies resulted in a healthy child; the exception resulted in the stillbirth of twins, for which no reason was found. Thus it appears that pregnancy may cause temporary suppression of reversible elements in sarcoid lung changes, with recrudescence after delivery, but otherwise has no effect on the course of the disease.

Discussion

The associations between erythema nodosum, bilateral enlargement of hilar lymph-nodes, and a good prognosis were first described by Löfgren (1953) and have been confirmed in Europe by several other investigators (Smellie and Hoyle, 1957, 1960; Hedvall, 1960; James, 1961), and in a preliminary account of my own experience (Scadding, 1956). On the other hand, Sones and Israel (1960), in Philadelphia, where 87% of their 211 patients were negroes, found that "progressive disease and death occurred almost as often among those whose initial roentgenogram of the chest showed only hilar adenopathy as among those who had pulmonary infiltration." Moreover, erythema nodosum was rare in their series, being observed in only 6 (3%) of their patients. Thus there is in this respect an important difference between the behaviour of sarcoidosis in the North American negro and in the European.

Whether there is a difference in prognosis between patients with pulmonary infiltration who do and do not have evidence of a preceding stage of hilar-node enlargement remains uncertain. I have given reasons above for the view that in some cases there is in fact no such stage, even though it cannot be denied that in some patients who, when first observed, show only pulmonary infiltration, hilar lymph-nodes may have been enlarged in the past. Although 58% of patients who had evidence of hilar node enlargement (group 2) attained clear chest radiographs as compared with 43% of those who had

no such evidence (group 3), this difference is not significant. It is not unexpected that erythema nodosum should have been reported in the past in seven of those with, and in only one of those without, hilar node enlargement; indeed, it may well be that the latter case was one of those included in group 3 because a stage of hilar node enlargement which in fact occurred was not detected. But the incidence both of eye lesions (8% as compared with 22%) and of skin lesions (11% as compared with 20%) was notably lower in group 3 than in group 4, suggesting that patients without a stage of hilar node enlargement may represent a group in which the disease tends to remain confined, at least so far as its clinical manifestations are concerned, to the lungs.

No useful comparisons can be made between mortality rates in reported series without knowledge of the proportions of various types of cases which they include. This is likely to vary with a number of factors. In a community where routine radiography of apparently healthy populations is frequent, more individuals with symptomless intrathoracic sarcoidosis following a benign course will be discovered than in one where radiography is less widely used. Series collected from the records of diagnostic chest clinics are likely to include fewer cases with established fibrosis and more with symptomless hilar lymph-node enlargement than those derived from hospital in-patient records. Thus, Ten Have (1958) estimated mortality at only 2% among 700 cases collected from the records of chest clinics in Holland; while Nitter (1953) found that of 90 patients observed in hospitals in Oslo, 13 (14.4%) died of sarcoidosis.

My own series cannot be regarded as representative of sarcoidosis in the community as a whole, for many of the cases in group 4 were referred to me from other physicians because they were not doing well. Since the mortality observed in any series is likely to be influenced greatly by the proportions of group 1 and group 4 cases included in it, estimates of the mortality of patients found to have lung involvement in a pre-fibrotic stage are more likely to be comparable from series to series than figures for the observed mortalities of whole series. Perhaps an approximation to such an estimate can be deduced from the proportion of those patients observed with pre-fibrotic lung changes who proceeded to fibrosis, and the proportion of those first observed in a fibrotic stage who died while under observation. Adding the 10 patients in group 1 who developed radiographic shadows in the lungs to the 40 in group 2 and the 37 in group 3, we have 87 patients who were observed with pre-fibrotic lung changes; reviewing the condition of these at the end of five years' observation, I estimate that 25 would have been placed in group 4 had they first been seen at that time.

Since 6 of the 27 patients in group 4 with established fibrosis died during the five years' observation, it can be deduced as a tentative estimate that between 6% and 7% of patients with sarcoid infiltration of the lungs in a pre-fibrotic phase are likely to die as a consequence of the disease within 10 to 15 years. Among patients with disabling fibrosis, liability to death due entirely or in part to the effects of sarcoidosis must be expected to continue throughout life; as noted above, 3 more of the 136 patients included in this review have died after the end of the five years' observation. Thus the total mortality must be expected to be higher than that estimated for even a prolonged but limited period from the first detection of lung infiltration. Smellie and Hoyle (1960) give a rather similar estimate to mine of the mortality of patients with pulmonary infiltration; from Fig. 3 of their paper it may be calculated that their estimate is rather over 9%, though it is difficult to relate this figure to any specified period.

Sones and Israel (1960), using the life-table method, calculated that the survival rate for their patients 10 years after diagnosis was 84.8%, compared with a normal expectancy of 95.2%, suggesting a mortality of about 10% from sarcoidosis within 10 years. As noted above, their series included 184 negroes, among whom 50 deteriorated during the observation period and 20 died, and 27 patients of European stock among whom only 4 deteriorated and none died. The difference between the proportions deteriorating was significant at the 5% level, confirming the general impression that the disease runs a less favourable course in North American negroes than in Europeans. It is probable that the high mortality reported in several series from the United States is due to the worse prognosis among negroes. Thus, Reisner (1944), in New York, found that 7 (25%) of 28 patients, the large majority negroes, died during observation for an average period of five years; and Riley (1950), also in New York, reported 10 deaths (19%) among 52 patients, of whom 41 were negroes.

In relation to the effect of extrathoracic changes on the prognosis, similar trends were found by Sones and Israel (1960) to those shown in my series. They found that cutaneous involvement was the feature most closely associated with progressive and fatal sarcoidosis; and that this association remained significant regardless of race. They also found no correlation between prognosis and eye involvement. Smellie and Hoyle (1960) found a trend towards a worse prognosis with a greater number of extrathoracic organs involved, but this trend fell just short of significance. Although Sones and Israel found a significantly worse prognosis in patients with three or more systems involved, this difference disappeared if patients without skin involvement were analysed. The high mortality reported by Gilg (1955) in a series of 191 patients with skin sarcoidosis in Copenhagen is of interest in this connexion. Thirty-seven of them were known to have died; 20 (10.5%) were proved to have died of heart failure due to pulmonary sarcoidosis, and eight from other known causes unrelated to sarcoidosis, while in nine it was not certain whether sarcoidosis had contributed to the cause of death.

Summary

A total of 136 patients with sarcoidosis involving the hilar lymph-nodes, the lungs, or both these structures were first seen in London between 1937 and June, 1955. The condition of the lungs of these patients five years after they first came under observation is reported.

They are divided into four groups according to the intrathoracic changes at first observation.

Group 1: enlarged hilar lymph-nodes only—32 patients, first seen at an average interval of six months from the apparent beginning of the disease.

Group 2: hilar nodes and lung shadowing—40 patients first seen at average interval of 18 months from the apparent onset.

Group 3: lung shadowing without available evidence of hilar lymph-node enlargement—37 patients first seen at an average interval of 21 months from the apparent onset.

Group 4: fibrosis judged to be already present—27 patients, first seen at an average interval of five and a half years from the apparent onset.

In group 1 the good prognosis reported previously was confirmed. After five years 27 patients (84%) had clear chest radiographs and 31 (97%) were free from symptoms. Only one patient had appreciable disability.

In group 2 23 patients (53%) had attained resolution of all radiographic shadows; another 2 (5%) had some residual radiographic abnormality but no symptoms; and 11 (28%) had radiographic abnormalities with only mild symptoms. Only 3 (7.5%) had moderately severe symptoms interfering with normal life. One had died of an unrelated cause.

In group 3 16 patients (43%) had attained radiographic resolution; 6 (16%) had some residual changes with no disability; 8 (22%) had residual changes with slight disability; and 6 (16%) had moderate disability. One had died of an unrelated cause.

In group 4 six patients died of pulmonary fibrosis due to sarcoidosis in the sixth to twenty-fifth year of the disease. One died of an unrelated cause. Of the remaining 20, 10 remained unchanged, 7 showed some improvement, and 3 became worse during the five years' observation.

Only a minority of the patients were treated with corticosteroids. Reasons are given for the conclusion that this measure did not affect the principal criterion of prognosis adopted—the attainment and maintenance under prolonged observation of a normal chest radiograph.

An onset with erythema nodosum was found to be associated highly significantly with a good prognosis.

Sarcoid skin lesions were significantly associated with a poor prognosis for the lung changes.

Sarcoidosis of the eye, generalized lymphadenopathy, and palpability (as opposed to gross enlargement) of the spleen did not seem to affect the prognosis of the lung changes.

Twelve pregnancies occurred in 10 women during the observation period. During four of these pregnancies shadows in the lungs cleared, only to return after delivery. Apart from this, the pregnancies appeared to have no effect on the course of sarcoidosis.

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The Royal Scottish Nursing Home in Edinburgh, which was taken over by the Nuffield Nursing Homes Trust in May last year, has now been officially reopened. It has been completely modernized and can now accommodate 48 patients. (*Scotsman*, September 29.)

THE BIRMINGHAM ORAL CONTRACEPTIVE TRIAL

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In March, 1960, the Birmingham Family Planning Association embarked on its first oral contraceptive trial. Its objects were twofold. First, in view of the existing widespread dissatisfaction with conventional techniques of birth control, it seemed desirable to assess the efficacy and acceptability of the method among British women. Second, while the ability of relatively large doses of oral contraceptives to control fertility had been adequately established (Pincus *et al.*, 1958, 1960), there was next to no information about the effect of lower doses with regard to both the suppression of ovulation and the incidence and severity of side-effects. With these aims in mind—and that of reducing the substantial cost of the larger dosage—the Executive Council of the Birmingham F.P.A. decided to conduct a trial on a reasonably large scale and under carefully controlled conditions laid down and supervised by a specially enlisted Medical Advisory Committee.

Messrs. G. D. Searle and Co. Ltd. agreed to support the trial both financially and by supplying adequate quantities of the test material (norethynodrel) to the Medical Advisory Committee.

The following account reports findings obtained with the 2.5-mg. strength of tablet (1 OC trial). As soon as it became apparent that this dosage provided insufficient conception control, the strength of tablets taken by volunteers was increased to 5 mg. a day. Those who had not conceived up to this moment and wished to continue, as well as new volunteers not previously employed, were enlisted in further trials (2 OC and 3 OC), and to date no failures have occurred among women participating in either of these two trials in the prescribed manner. Where possible, provisional information about the results with the 5-mg. tablet is included, but a full report must be deferred until the 2 OC and 3 OC trials have been completed.

Subjects and Experimental Procedures

Selection of Participants

These were chosen from the large number of women who had responded to the appeal for volunteers. They had to satisfy the following criteria:

(*a*) *Age* under 36 years at the time of beginning the trial.